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BLOOD-BRAIN BARRIER WORKSHOP.(U)
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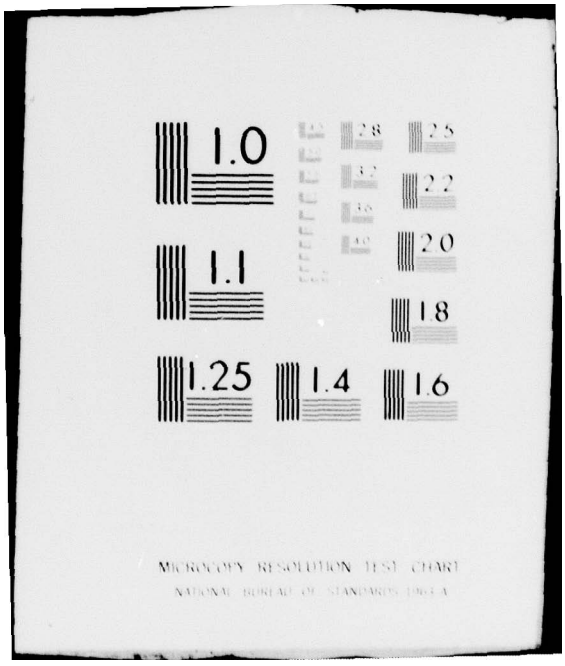
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BLOOD-BRAIN BARRIER WORKSHOP

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FOREWORD

Results of a workshop to consider the Blood-Brain Barrier in relation to microwave energy are presented. The report was prepared under Office of Naval Research Contract No. N00014-79-M-0005.

Participation in the workshop was provided by Dr. B. Graham and the interpretation, context, and organization of the report was the responsibility of Mr. M.H. Benedick.

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BLOOD-BRAIN BARRIER WORKSHOP

INTRODUCTION

A workshop was conducted on October 30-31, 1978 at the Maryland Inn, Annapolis, Maryland to review and evaluate research performed on the blood-brain barrier in experimental animals exposed to microwave energy. The workshop was sponsored jointly by the Office of Naval Research and the Naval Medical Research and Development Command for the Tri-Service Electromagnetic Radiation Panel (TERP).

The purpose of the workshop was: to review and discuss reported research on the effect of microwave fields on permeability of the blood-brain barrier; to provide recommendations on whether additional research in the subject area is required--and if required, to suggest design guidelines for studies that would address the question of blood-brain barrier effects due to microwaves; and to evaluate the possible hazards to personnel that such effects might produce.

A number of investigators presented their work in the subject area and the works of many others were discussed.

THE BLOOD-BRAIN BARRIER

Capillaries in the brain regulate transport of substances between the blood and the surrounding neuropil by selectively allowing transport of molecules across the capillary wall. This selective process acts as a regulatory barrier to certain substances and is, therefore, called the blood-brain barrier.

It is believed the barrier is formed by endothelial cells that line the interior of the blood vessels. These cells are joined by tight junctions. It is these tight junctions that partially form the morphological basis of selectively regulating the passage of larger molecules across the capillary walls. In addition, lipid solubility and the polar nature of molecules are important considerations in determining which substances are transported across the endothelial membranes.

The barrier's permeability to normally restricted substances can be increased by infusion into the bloodstream of a substance that increases the osmotic pressure of the blood. Barrier permeability can also be increased by hydrostatic pressure. Barrier permeability is increased by endothelial cell shrinkage that opens the tight junctions between them thus allowing the large molecules not normally diffusible to pass through. If the barrier is not opened too wide and too long, the barrier opening is reversible and the endothelial cells will return to

normal shape and size and the tight junctions once again will regain their integrity. If no damage is caused to the endothelial cells, if cerebral circulation is not compromised, and if cerebral oxygenation is maintained, reversible barrier opening is possible without damage to the brain by edema or infiltration of toxic molecules.

RESEARCH RESULTS

A. General

As noted by Justesen and Albert in their presentations at the workshop, the early history of knowledge concerning selective intercellular diffusion can be traced to 1885 when Ehrlich[1] noticed that trypan blue dye introduced into the bloodstream stained all body organs except the brain and spinal cord. This observation was confirmed and extended by Goldman[2] and out of this grew the concept of the blood-brain barrier. Confirmation of such a barrier was not established, however, before the work of Wallace and Brody[3,4] in 1939 and that of Bakay[5] in 1956. More recently, Rapoport[6] has shown an increase in cerebrovascular permeability as a result of osmotic treatment. The recent work of Pappius[7] has also shown increases in cerebrovascular permeability produced by osmotic and injury-induced opening of the blood-brain barrier. Injury-induced openings were accomplished by freezing heat-induced lesions.

B. Microwave

Frey et al.[8] reported an increase in blood-brain barrier permeability of rats exposed to low power pulsed or CW microwave energy at 1.2 GHz. The CW power level was 2.4 mW/cm^2 and the pulse modulated power level was 2.1 mW/cm^2 peak and 0.2 mW/cm^2 average at 1000 pulses per second. Five groups of rats that differed in head position with reference to the energy source were exposed and a sixth group was not exposed. Fluorescein dye injected into the bloodstream resulted in brain tissue staining in four of the exposed groups. Significant brain staining did not occur in one exposed group and in the unexposed group. The pulse modulated signal was 2.5 times more effective than the CW signal in opening the barrier although the average power level was one tenth that of the CW signal. Frey[9] reported confirmation of Albert's[13] earlier report on the barrier opening in the eye which has a blood-barrier system that functions in a manner similar to that of the blood-brain barrier. Frey found significantly more fluorescein staining of the vitreous humor of the eye in rats exposed to pulsed microwave energy at a peak power level of 75 mW/cm^2 and at a frequency of 1.2 GHz as compared to that of unexposed rats. Frey[9] also studied effects of 60 Hz electric fields on the blood-brain barrier of rats. Exposure was to a vertical CW electric field at 3.5 kV/m for 17 to 40 days. There were no significant differences in fluorescein dye staining of brain tissue between exposed and unexposed rats.

Oscar and Hawkins[10] were unable to replicate Frey's results on the blood-brain barrier after exposing rats to 1.2-GHz energy. Their results were too variable using fluorescein dye as the indicator. The dual radioactive isotope technique of Oldendorf, which uses tritiated water as a diffusible internal standard, was then used. This experiment showed an increase in blood-brain barrier permeability for rats exposed to microwave energy at a frequency of 1.3 GHz. The largest changes in the brain uptake index (BUI) occurred in the medulla; smaller, but significant BUI's occurred in the cerebellum and hypothalamus. Blood-brain barrier permeability to three saccharides having different molecular weights and negligible uptake in brain tissue under normal conditions was also studied. Increased BUI's occurred in all three brain regions for mannitol and inulin after exposure to microwaves, but there were negligible increases for dextran. The duration of microwave induced change of permeability, so indexed by BUI, was also studied. Increased BUI's existed at 8 minutes and at 4 hours after exposure, but not after 24 hours. Both CW and pulsed microwave signals were used in this study. The general trend shown by the data was increased permeability with increasing microwave power for both CW and pulsed signals up to the region of 0.5 to 2 mW/cm^2 where the permeability change leveled off and then began to decrease with further increase in power. The data also showed in general that the average power density required to produce a given change in barrier permeability was higher for CW than for pulsed signals. Thus, this study confirmed the findings of Frey et al. that changes in blood-brain barrier permeability can be produced by exposure to microwaves at average power densities below 10 mW/cm^2. However, the dual radioactive isotope technique of Oldendorf, used in this study to quantitatively measure barrier permeability, has certain limitations. Many parameters such as blood flow, blood volume, metabolic rates, barrier permeability, etc. can account for measured changes and therefore, it cannot be assumed that any measured change is only a change in barrier permeability. Oscar has since adapted the dual compartment technique developed by Rapoport to measure cerebrovascular permeability. This technique is also not without limitations but may be preferable to Oldendorf's procedure. Study in this area is continuing with emphasis placed on whether reported changes in barrier permeability are actually changes in permeability or result from changes in the various other parameters (e.g., circulatory flux) involved in the measurements.

Sutton[11] has studied effects of microwave induced hyperthermia on blood-brain barrier permeability in rats in his research dealing with treatment of brain tumors. Brains of rats have been preferentially heated by 2.45 GHz microwaves. When the body temperature was maintained at the normothermic level of 37 ^{o}C, barrier disruption to a tracer protein (horseradish peroxidase) occurred after 10 minutes at a brain temperature of 45 ^{o}C and, after 15 minutes, at a brain temperature of 42 ^{o}C. In an effort to preserve the integrity of the barrier, thus allowing the brain to be heated safely for longer periods of time, data were obtained on initially hypothermic rats. When the body temperature

was maintained at a hypothermic level of 30 °C, barrier integrity was not lost until 15 minutes had elapsed at a brain temperature of 45 °C, and until 30 minutes at a brain temperature of 42 °C. Protection of the barrier by cooling of the lower body was most pronounced when the brain temperature was elevated only to 40 °C. Barrier integrity was lost in normothermic rats after about one hour of microwave-induced heating of the brain to 40 °C, while this did not occur in hypothermic rats until two to three hours had elapsed when the brain temperature was the same. Sutton concludes that microwaves are capable of disrupting the blood-brain barrier; disruption is dose related, and depends on the elevation of temperature and the duration of elevation.

Albert[12,13] studied effects of microwaves on blood-brain barrier permeability in histological specimens using light- and electron-microscopy. Chinese hamsters were exposed at 10 mW/cm^2 to 2.45 GHz CW energy. Following exposure, the animals were given an injection of a protein (horseradish peroxidase), which yields a reddish-brown reaction product when the tissue is exposed to diaminobenzidine. The presence of this reaction product outside the blood vessels of the brain indicates areas of barrier penetration. In both exposed and control animals, some areas of the brain displayed barrier penetration. These areas were the pineal gland, median eminence, area postrema, tuber cinerium, paraphysis, the wall of the optic recess, and the eminentia saccularis. But in other areas of the brain, the reaction product was generally present in neuropil of significant numbers of exposed animals and absent in most unexposed animals. Reaction product was scattered in random parts of the brain and was not localized in any functional region. The results show that acute exposure to 10 mW/cm^2 energy altered the blood-brain barrier's permeability to horseradish peroxidase. Albert[13] extended this work to include the study of possible reversibility of the microwave-induced change in barrier permeability. Wistar rats and Chinese hamsters were exposed at 10 mW/cm^2 to 2.8 GHz CW energy. The light and electron microscopic tracer techniques were also used in this study. Results indicated that the microwave-induced increase in blood-brain barrier permeability showed a significant reduction one hour after exposure and returned to normal approximately two hours afterward. Since the measured increase in hypothalamic temperature in rats exposed at 10 mW/cm^2 averaged 0.4 °C, the increase in barrier permeability may not have been due to hyperthemia. Also, the results of this study show that an increase in blood-brain barrier permeability induced by short term microwave exposure is a reversible phenomenon.

Spackman et al.[14] studied the blood-brain barrier in mice exposed to 918 MHz energy. Average power levels were 2.5 and 33 mW/cm^2 for both a CW field and a pulse modulated field of 10 microsecond pulses at 100 pulses per second. CW energy at a power level of 132 mW/cm^2 was also used in this study. Indicators of barrier permeability were fluorescein dye and several unphysiologic amino acids not normally found in the brain. No evidence of increased barrier permeability could be detected

although there were significant elevations of temperature in mice exposed at 132mW/cm^2. Mice were also exposed to 30 MHz CW energy at 1, 5 and 10 V/cm, but no effect was observed on the blood-brain barrier's permeability.

Merritt and Chamness[15] attempted to replicate the findings of Frey et al.[8] and Oscar and Hawkins[10], in which there was a reported increase in barrier permeability in rats exposed to 1.2 GHz.

Under similar exposure conditions and using fluorescein dye as the indicator, Merritt reported no effect on barrier permeability. Merritt's data has since been analyzed by Justesen and the conclusions are being restudied.

Preston[16] investigated the effect of 2.45 GHz CW microwave energy on blood-brain barrier permeability. The Oldendorf radiotracer method was utilized and the brain uptake indices were calculated to determine the permeation by radiolabeled test substance into brain regions relative to that of a tritiated-water reference. Rats were exposed in one series of experiments at 0.1, 0.5, 1, 5, and 10 mW/cm^2 and in a second series of experiments at 0.3, 1, 3, 10, and 30 mW/cm^2. Care was taken to minimize both circadian influences and differences in injectate composition. There was no statistically reliable indication of a microwave effect on the blood-brain barrier at any level of power density. There were no significant differences between the brain uptake index values for exposed rats and those not exposed. The data showed that the higher brain uptake index values in cerebellum and medulla relative to cortex and diencephalon were a result of a higher background content of the radiolabeled test substance and a much lower content of the tritiated water reference substance. This suggests that substances injected into the carotid artery reach only a portion of the cerebellum and medulla because some of the arterial supply to these brain regions originates in the vertebral arteries. It is probable that tissue supplied both by the vertebral and by the carotid arteries is being analyzed in brain uptake index measurements of the cerebellum and medulla. Therefore, because of the vertebral blood supply to these brain regions, changes of BUI's could be misinterpreted as an alteration in barrier permeability to the ^{14}C-test substance, mainly present as intravascular contaminant, when in fact an altered uptake or retention of the tritiated water reference substance had occurred. It appears that data on radioisotope distribution is a very important part of any experiment in which BUI measurements are made in these brain regions.

The majority of the blood-brain barrier permeability studies using microwaves were performed on smaller animals such as mice, hamsters, and rats. However, Chang et al.[17] have used dogs in studies of microwave effects on the blood-brain barrier. A technique involving multiple sampling of cerebrospinal fluid and plasma was utilized and the distribution ratio of an administered radiotracer was determined as a measure of

diffusion across the blood-brain barrier. Heads of dogs were preferentially exposed in the near field of a microwave horn for 20 minutes to 1.0 GHz CW microwave energy at power levels of 2, 4, 10, 50 and 200 mW/cm^2. Two dogs were exposed at each power density level. No effect on barrier permeability was noted in any of these test subjects. However, data from a group of 11 dogs exposed at 30 mW/cm^2 showed an increase in barrier permeability in four out of eleven dogs. The author indicated that these results point to a microwave "amplitude window" effect which may be operating near 30 mW/cm^2 for the dog. However, because of inequality of sample sizes there was little support for this interpretation among the Workshop's participants. The deviant dogs may have shown evidence of marked individual differences, but these differences could not be confirmed in view of small samples studied at other power densities.

Discussion

The literature concerning microwave effects on the blood-brain barrier includes application of various microwave and RF frequencies, one study at 60 Hz and a variety of radiated power levels. In addition, several techniques have been used to evaluate possible effects on blood-brain barrier permeability. Test results from the individual studies cannot be directly combined mathematically to improve upon the statistics because of the diversity of parameters used in the various studies. However, because of the variety of experimental protocols used in this research, the literature gives us some background information on possible effects of microwaves on the barrier. Unfortunately, the body of literature on the subject does not provide a conclusive scientific answer to the question of possible microwave effects on the blood-brain barrier. While Preston[16] showed no significant effect on permeability, attempted replication of certain studies that showed effects on permeability have produced conflicting results. For example, Oscar and Hawkins[10] confirmed Frey's[8] positive results, but Merritt and Chamness[15] could not replicate the positive findings of either Frey or Oscar and Hawkins. In addition, Merritt's conclusion of negative findings a propos fluorescein uptake by rats after exposure to a 1.2 GHz field are apparently at odds with his data[25].

As noted by Justesen at the conclusion of the workshop, there is a need for improved methodology in blood-brain barrier research. One possible problem in much of the research is the choice of anesthetic agent. Work reported by Angel and Lafferty[19] indicates that pentobarbitol increases the blood-brain barrier permeability and yet it was used in many of the microwave studies on integrity of the barrier. The techniques normally used to measure altered permeability are not sufficiently developed to the point where test results are not questioned. The intravenously injected flourescein dye technique yields results that are more qualitative than quantitative[20]. The brain uptake index technique of Oldendorf and the indicator dilution technique might yield results which are misinterpreted

because of changes in cerebral blood flow. In addition, effects on brain regions cannot be isolated, and they are not sensitive enough to detect subtle changes in permeability coefficients[21]. The dual compartment technique developed by Rapoport is not subject to these limitations[21]. However, the measure determined by the Rapoport method is actually PxA where P is permeability and A is vessel cross-sectional area, and is thus indirect. This technique has been used by Oscar who is not sure this technique is sensitive enough to measure subtle changes in cerebro-vascular permeability[22]. Albert[25] suggested that Rapoport's technique might have serious limitations unless correction is made for capillary space.

The majority of research has been done on albino laboratory animals. Creel et al.[23,24] have reported that for all mammals studied in their laboratory, albinism is associated with neuroanatomical and neurochemical defects of the cerebrum. The question arises whether effects on the blood-brain barrier in normally pigmented animals would be the same as in albino animals.

The use of small laboratory animals in blood-brain barrier research has several disadvantages in terms of translation of test results to assess microwave effects on humans. The first of these is the fact that the skull of the rats is thin compared with larger animals and humans which could result in different amounts of radiated energy reaching the brain. Another reason the data from small laboratory animals may not be relevant to humans is that at least in some studies the microwave frequency employed is close to the resonant frequency of the rat. This factor may make translation of the test results to humans very difficult. Use of large animals would also permit longitudinal studies since repeated measurements may be taken from the same animal without the need to sacrifice the animal.

Exposure conditions are not adequately defined in most of the microwave studies reported in the literature. Proper specification of exposure conditions is essential for at least two reasons. One reason is that a study can complement other studies in the subject area only if it is known which studies represent similar exposure conditions. The second reason is results of the research can only be applied to actual real-world situations if the exposure conditions are known. In order to properly define exposure conditions, it is necessary to utilize both densitometry and dosimetry. Laboratory simulation of microwave environments should provide for the test subject being in the far-field of the generated signal. Test chambers should include sufficient absorbent material to minimize standing waves and allow accurate power density measurements of the incident field to be made. But densitometry alone cannot fully define the exposure conditions. It is also necessary to include dosimetric measures for information on energy absorption and anatomical distributions of absorbed energy. Complete definition of the exposure conditions for every study is very important if the true significance of the study is to be realized. This is also a very

important consideration for the eventual task of extrapolating from the test results on small laboratory animals to predictions of effects on humans.

There is a great need for better experimental design in blood-brain barrier research involving electromagnetic fields. It is true that there is much to be learned about the barrier. However, what is known should be utilized in designing experiments. Hypotheses should be based on theory and experiments should be designed to evaluate these hypotheses. Mechanisms need to be formulated and evaluated. Adequate statistical analyses should be incorporated into every experiment. It would seem advisable to include in the design a comparison between diffusion into body cells where the tracer has easy access and diffusion of the tracer into brain cells.

Also, an anesthesia that does not cause, directly or indirectly, a change in barrier permeability should be selected for these studies. Positive controls should be used to test the sensitivity of the experimental protocol.

Conclusions

Several conclusions can be drawn from the presentations and discussions during the workshop. The first is that from a scientific point of view, much more research needs to be done to understand the structure and function of the blood-brain barrier and to evaluate the implications that an increase in barrier permeability would evoke. Experiments should be designed to obtain scientifically sound data so that quantitative answers to these questions can be found.

The second conclusion is that there is no indication of impending danger to the blood-brain barrier from exposure to low level microwaves, i.e., on the order of 1 mW/cm^2 for short periods of time. Replication of studies that disclosed positive findings has not always verified the earlier findings. Oscar and Hawkins[10] confirmed the positive results of Frey[8] using an improved measurement technique. Since then Oscar has questioned the interpretation of these results because the measurement technique used in his study may not account for all of the changes in the various parameters allied with the noted changes. Sutton[11] found positive effects on the blood-brain barrier when temperature of the brain was elevated from 37 °C to 40 °C by applying microwave energy to the brain. Albert[12,13] found positive effects on barrier permeability for microwave exposure of 10 mW/cm^2 which increased the brain temperature by 0.4 °C. However, Preston[16] could find no evidence of penetration of radiolabeled substance using the Oldendorf method at exposure levels up to 10mW/cm^2. There appears to be no theoretical or experimental evidence that low level microwaves that do not raise the brain temperature could be expected to affect the integrity of the barrier. It can

be reasonably concluded that if a real potential for catastrophic effect exists, it would be evident from the research already reported in the literature.

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BLOOD-BRAIN BARRIER WORKSHOP
30-31 OCTOBER 1978
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BLOOD-BRAIN BARRIER WORKSHOP
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PROGRAM

30 OCTOBER

Opening Comments	POSTOW/ROZZELL
The Structure and Function of the Blood-Brain Barrier	RAPOPORT
Effects of Opening of Blood-Brain Barrier on Local Cerebral Glucose Utilization	PAPPIUS
COFFEE BREAK	
Regional Cerebral Blood Flow and Blood-Brain Barrier Permeability After Low-Level Microwave Exposure	GRUENAU/OSCAR
Eye and Brain Barriers to Fluorescent Dye	FREY
Studies on the Blood-Brain Barrier: Absence of an RF Effect	RILEY/SPACKMAN
LUNCH	
Uptake of L-Phenylalanine in Microwave Irradiated Rats	MERRITT
Brain Uptake Index Measurements of Manitol Penetration Across the Blood-Brain Barrier in the Rat Following 2.45 GHz Microwave Irradiation	PRESTON
Effect of 1 GHz Microwave Radiation on the Blood-Brain Barrier of Dogs	CHANG
COFFEE BREAK	
The Effect of Microwaves on the Rat Blood-Brain Barrier to Horseradish Peroxidase	SUTTON
The Current Status of the Blood-Brain Barrier and Microwave Interactions	ALBERT

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Non-Ionizing Radio-Frequency Electromagnetic Radiation and the Blood-Brain Barrier: A Synthesis	JUSTESON
COFFEE BREAK	
Discussion, Analysis, and Recommendations	ALL